REMARKS

Claims 8, 19, and 20 are cancelled without prejudice. New claims 25 is added. Claims 1, 2, 9-10, 12-16, and 21-24 are amended. The amendments to claims 1, 2, 9-10, 12-16, and 21-24 find support at least at paragraph [0034] to [0037] of the published application. New claim 25 finds support at least at paragraph [0033]. With entry of this amendment, claims 1-7, 9-18, and 21-25 will be pending. No new matter has been entered by way of these amendments.

Rejections Under 35 U.S.C. § 103 (a)

Claims 1-4, 6-18 and 21-24 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,444,234 to Kirby et al. ("Kirby"), in view of WO 02/40033 to Tocovite Party Ltd. ("Tocovite"), and further in view of U.S. Patent Pub. 2003/0157326 to Vaghefi et al. ("Vaghefi").

Kirby discloses pharmaceutical compositions for the transdermal administration of a medicament, or other active agent, by topical application of the composition to the skin of humans. Abstract. The pharmaceutical compositions are formulated to provide for very rapid uptake of the medicament and transmigration into and through the skin to either fatty tissues or the vascular system, while minimizing irritation to the skin and/or immunological response. Abstract. The pharmaceutical compositions are based on a transdermal delivery system (TDS) wherein the medicament is modified to form a true solution in a complex formed from particular solvents and solvent and solute modifiers in combination with skin stabilizers. Abstract.

Tocovite discloses an emulsion composition comprising a particular equimolar amount of a mono-electron transfer agent phosphate derivative (e.g., mono-tocopheryl phosphate), a di-electron transfer agent phosphate derivative (e.g., di-tocopheryl phosphate), and a suitable carrier. Abstract. The phosphorylated electron transfer agents may be complexed with a complexing agent selected from amphoteric surfactants, cationic surfactants, amino acids having nitrogen functional groups and proteins rich in these amino acids. Tocovite at 4.

Vaghefi teaches pharmaceutical compositions comprising microspheres with a water insoluble organic matrix in an interior region, throughout which are dispersed a plurality of microcapsules containing hydrophobic bioactive compounds. Abstract. The microcapsules located in the interior of the microspheres are coated with pharmaceutically-acceptable, charged (hyrdophilic) materials, thereby providing facilitating the transport of the hydrophobic bioreactive compounds. See Abstract, paragraphs [0014] to [0019].

Applicants respectfully disagree that one of skill in the art would be motivated by the prior art to produce the formulation of independent claim 1. While Tocovite discloses phosphorylated electron transfer agents for the treatment of skin conditions, Tocovite does not teach or suggest, nor provide any motivation, to include alkaloids in those formulations, let alone to produce a reaction product of one or more alkaloids having a tertiary amine with one or more phosphorylated electron transfer agents, as is recited in claim 1. Neither Kirby nor Vaghefi cure the deficiencies of Tocovite. In fact, Kirby and Vaghefi both teach away from the formulation of independent claim 1. That is, both Kirby and Vaghefi teach that additional components or methods are necessary to achieve efficient transdermal transport of alkaloids

Kirby is directed to topical formulations comprising (1) an active agent; (2) a solvent system in which the active is agent is soluble; and (3) a substance capable of *in vivo* stimulation of cyclic adenosine monophosphate (CAMP) or cyclic guanosine monophosphate (CGMP). Kirby, col. 6, ln 21-26. The solvent system of Kirby consists of a solvent, a solvent modifer, and a solute modifier. Kirby, cols. 9-11. The solvent is typically a lower alcohol or an organic solvent. Kirby, col. 10, ln. 8-16. The solvent modifer is typically a polar molecule used to make the active ingredient more soluble through van der Waals forces or hydrogen bonding. Kirby, col. 10, ln. 45-68. The solute modifer is a compound which further facilitates the solubility of the active by forming reversible or temporary complexes with the solute. Kirby, col. 11, ln. 34-43. As the examiner concedes in the Office action, there is no teaching in Kirby that phosphorylated electron transfer agents may be used as solvent modifiers or solute modifiers. Office action at 4. Applicants respectfully submit that there is no suggestion that phosphorylated electron transfer agents may be used as solvent modifiers or solute modifiers either. There is simply no discussion of phosphorylation processes, nor how phosphorylation may improve the solubility of alkaloids.

Furthermore, Kirby teaches that it is necessary to include substances capable of *in vivo* stimulation of CAMP or CGMP in the transdermal formulations because transporting substances through the skin results in chemical cascades that consume large amounts of energy. Kirby, col. 12, ln. 23-39. Adding energizing molecules to the formulation increases the likelihood that the active ingredient will reach its target and be utilized by the body. Kirby, col. 12, ln. 23-39. Compositions lacking these energizing molecules can lead to sensitization, ACD, or anaphylaxis. Kirby, col. 12, ln. 32-34. In other words, absent these energizing molecules, one of skill in the art viewing Kirby would not anticipate successful formulations if those formulation did not have energizing molecules. As the examiner will note, claim 1 does not recite energizing molecules, nor are such energizing molecules taught anywhere in the present application.

Because Kirby teaches that such energizing molecules are necessary to avoid sensitization, etc., Kirby teaches away from the formulation of claim 1.

Like Kirby, Vaghefi does not teach or suggest a formulation comprising the reaction product of one or more alkaloids having a tertiary amine with one or more phosphorylated electron transfer agents. In fact, Vaghefi teaches that delivering alkaloid species, such as codeine, transdermally requires elaborate microsphere structures to assure that the hydrophobic compounds can be transported across the dermal boundary. Vaghefi at [0014] to [0017]. Because Vaghefi teaches the need for microspheres to facilitate the delivery of alkaloids, Vaghefi teaches away from claim 1, which recites the use of phosophorylated electron transfer agents (without microspheres) to facilitate the transport of alkaloid species such as codeine.

In summary, it is difficult to appreciate how one of skill in the art would find it obvious to combine Kirby, Tocovite, and Veghefi to arrive at the subject matter recited in claim 1. In order to do this, one of skill in the art would have to modify the solvent system of Kirby, which is a selected combination of solvents, solvent modifiers, and solute modifiers, to instead comprise phosphorylated electron transfer agents, but yet not include the energizing molecules taught as crucial to Kirby, nor the microsphere structures taught as crucial to Vaghefi.

Because Kirby and Veghefi teach away from the formulation of claim 1, Kirby and Veghefi cannot be used to provide motivation for one of skill in the art to modify the formulations of Tocovite to achieve claim 1. Accordingly, withdrawal of the rejection of claim 1 under 35 U.S.C. § 103(a) is respectfully requested.

Claims 2-7, 9-18 and 21-24 depend from allowable independent claim 1, and are therefore allowable. Claims 2-7, 9-18 and 21-24 may also contain additional patentable subject matter for reasons not stated herein. Withdrawal of the rejections of claims 2-7, 9-18 and 21-24 under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance. Favorable consideration of the present application as amended is therefore respectfully requested. If a conference call would be useful in resolving issues arising from the filing of this communication, please contact the undersigned at the below-noted number.

Respectfully submitted,

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